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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/052,121	01/17/2002	Cato T. Laurencin	DRE-0067	1682

7590 05/31/2006

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EXAMINER	
NAFF, DAVID M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 05/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/052,121	LAURENCIN ET AL.	
	Examiner	Art Unit	
	David M. Naff	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5 and 6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/22/06 has been entered.

An amendment of 3/22/06 amended claim 1.

Claims examined on the merits are 1-3, 5 and 6, which are all claims in the application.

Claim Rejections - 35 USC § 112

Claims 1-3, 5 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are confusing and unclear by "several minutes" in line 5 of claim 1 being uncertain as to meaning and scope. A number of minutes that are "several" will be relative and subjective. It is suggested the claim recite "heating at a sintering temperature that is above the glass transition temperature of the polymer and below the melting temperature of the polymer" as described in the specification (paragraph bridging pages 8 and 9).

Claim Rejections - 35 USC § 103

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Starling et al (6,210,715 B1) in view of Crotts et al (Journal of Controlled Release).

The claim is drawn to scaffold for tissue engineering comprising biodegradable polymer-based hollow microcarriers with a density equal to or less than water bonded together by heating at several degrees above the glass transition temperature of the polymer into a three dimensional scaffold with a density equal to or less than water and a fully interconnected pore network. The scaffold exhibits cell attachment and retains cell phenotype upon in vitro culturing with cells in a rotating bioreactor.

Starling et al disclose microcarriers (also referred to as microspheres or microbeads) that can be used for cell culture (col 4, lines 32-35, col 5, lines 1-7 and col 6, lines 32-35), or as an implant as a carrier of a pharmaceutical agent (col 9, lines 15 and 22, and col 9, line 57). The microspheres can be hollow, and be bonded together to form an aggregate of bonded together hollow microspheres (Figure 1-1 (1.4)). The hollow microspheres have a density of less than 1 gm/cc (col 6, line 54), and are bonded together by coating with calcium phosphate (CaP) and sintering to provide an aggregate having a density of about 1.00-1.12 gm/cc (col 6, line 60), preferably about 1.00-1.06 gms/cc (col 4, line 58). The hollow microspheres are made of a substrate, which can be calcium phosphate, glass, other oxide ceramics or polymers, proteinaceous materials or

composite materials (col 5, line 66 to col 6, line 2). When the substrate material is polymeric or proteinaceous, bonding together of the hollow microspheres can involve heating the substrate material to soften the surface (col 6, lines 44-46). Polymeric/organic substrate materials for preparing the hollow microsphere include dextran, polyethylene, polypropylene, polystyrene, polyurethane and collagen (col 17, lines 36-39).

Crotts et al disclose preparing hollow microspheres composed of poly(D,L-lactic-co-glycolic acid) (PLGA) (page 91, abstract) that can be used as a carrier for drug delivery by encapsulating a drug (page 104, right col, lines 1-11). Poly(D,L-lactic acid) and its copolymers with glycolic acid are used as microsphere material due to their versatile biodegradability and biocompatibility (page 91, left col, under "Introduction"). The microspheres are prepared (page 93, left col, under "Microsphere preparation") by adding a water phase (with or without BSA (blood serum albumin)) to methylene chloride containing PLGA, generating an emulsion by ultrasonication, adding the emulsion to a PVA/PBS solution while being magnetically stirred, and continuing stirring for 2-3 h to permit evaporation of solvent. The microspheres are collected by centrifugation, washed and lyophilized, and size distribution is measured by using a series of stainless steel meshes.

It would have been obvious to use as the polymeric hollow microspheres of Starling et al, hollow microspheres made from PLGA as suggested by Crotts et al to obtain the property of PLGA having versatile biodegradability and biocompatibility as disclosed by Crotts

et al. It would have been expected the PLGA hollow microspheres can be bonded together to form an aggregate of hollow microspheres by procedures disclosed by Starling et al. The aggregate when shaped as disclosed by Starling et al (col 9, lines 50-58) will be a scaffold as presently claimed. Heating to soften the surface of microspheres to bond the microspheres together as suggest by Starling et al will result in using a temperature several degrees above the polymer glass transition temperature of the polymer. A scaffold resulting from modifying Starling et al as suggested by Crotts et al will inherently retain phenotype when culturing in vitro in a rotating bioreactor as claimed.

Response to Arguments

Applicants urge that there must be motivation to combine the teachings of the references. However, motivation has been set forth, i.e. to obtain the property of PLGA having versatile biodegradability and biocompatibility.

Applicants urge that Starling et al teach away from substituting with the microspheres of Crotts et al since the microspheres of Crotts et al do not contain calcium phosphate, and Starling et al disclose microspheres formed of calcium phosphate. However, while Starling et al may prefer microspheres formed using calcium phosphate, this is not critical and Starling et al disclose that the microspheres can also be made of a polymer as an alternative to calcium phosphate (col 5, line 66 to col 6, line 2). Coating with calcium phosphate as disclosed by

Starling et al can be omitted when heating to soften the surface of a polymer as disclosed by Starling et al (col 6, line 44-46).

Applicants urge that the substitution is not obvious since Crotts et al teach microspheres for controlled drug release instead of microspheres in aggregates for cell culture. However, the microspheres of Starling et al like those of Crotts et al can be made of a polymer, and due to the similarity of the polymer microspheres, it would have been expected the microspheres of Crotts et al will provide an aggregate by heating to soften the surface as disclosed by Starling et al. Furthermore, it would have been obvious to use the PLGA polymer of Crotts et al because of its versatile biodegradability and biocompatibility as the polymer used by Starling et al to prepare microspheres without forming a microsphere containing a drug as disclosed by Crotts et al.

Applicants urge that Starling et al teaches heating to at least 1000^0 C and disclose heating at 1100-1350^0 C for 0.1 to 6 hours, and such high temperatures cannot be used with polymeric microspheres. However, Starling et al disclose the alternative of heating to soften the surface of a polymer microsphere. Heating to soften the surface will not require a temperature of least 1000^0 C, but will require a temperature that can be used with polymeric microspheres.

Claim Rejections - 35 USC § 103

Claims 2, 3, 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claim 1 above, and further in view of Spaulding (6,001,643) or Granet et al (AJ on 1449).

Claims 2 and 3 require the scaffold of claim 1 to be seeded with cells via culturing *in vitro* in a rotating bioreactor.

Claims 5 and 6 require a method of generating tissue by seeding the scaffold of claim 1 with cells that produce the tissue, and culturing the seeded cells in a rotating bioreactor.

Starling et al and Crotts et al are described above.

Spaulding discloses culturing cells in a roller bottle for implanting to produce tissue. Microcarrier beads having densities less than the cell culture medium can be used for cell attachment to constrain tissue constructs to the area surrounding the annular axis and away from the cylinder wall of the bottle (col 16, lines 25-30).

Granet et al disclose culturing osteoblastic cells on microcarriers in a rotating-wall vessel (page 514, section 2.1.2).

When preparing the aggregate of bonded together hollow microspheres of Starling et al using hollow microspheres made from PLGA as suggested by Crotts et al as set forth above, it would have been obvious to use the aggregate for cell culture as suggested by Starling et al, and carry out cell culture in a roller bottle as disclosed by Spaulding or in a rotating-wall vessel as disclosed by Granet et al since these culturing techniques are intended for culturing cells on a carrier. It would have been further obvious to provide the aggregate with a density less than that of water as suggested by Spaulding so the aggregate will surround the axis away from the wall. Culturing cells such as osteoblast cells would have been obvious when the function of these cells is desired.

Response to Arguments

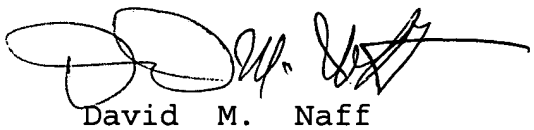
This rejection has not been separately traversed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is 571-272-0920. The examiner can normally be reached on Monday-Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



David M. Naff
Primary Examiner
Art Unit 1651

DMN
5/26/06